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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☑ Declaration Submitted With Initial Filing *OR* ☐ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	P01936US06
First Named Inventor	MARSHALL, William E.
COMPLETE IF KNOWN	
Application Number	
Filing Date	
Art Unit	
Examiner Name	

I hereby declare that:

Each inventor's residence, mailing address, and citizenship are as stated below next to their name.

I believe the inventor(s) named below to be the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

OLIGORIBONUCLEOTIDES ALERT THE IMMUNE SYSTEM OF ANIMALS TO THE IMMINENCE OF MICROBIAL INFECTION

(Title of the Invention)

the specification of which

☑ is attached hereto

OR

☐ was filed on (MM/DD/YYYY) [ ] as United States Application Number or PCT International Application Number [ ] and was amended on (MM/DD/YYYY) [ ] (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? Yes	No
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

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DECLARATION — Utility or Design Patent Application

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF SOLE OR FIRST INVENTOR: ☐ A petition has been filed for this unsigned inventor			
Given Name (first and middle [if any]) William E.		Family Name or Surname Marshall	
Inventor's Signature William E. Marshall			Date 3-12-04
Residence: City Naples	State Florida	Country USA	Citizenship USA
Mailing Address 155 1st Avenue South			
City Naples	State Florida	ZIP 34102-6946	Country USA
NAME OF SECOND INVENTOR: ☐ A petition has been filed for this unsigned inventor			
Given Name (first and middle [if any])		Family Name or Surname	
Inventor's Signature			Date
Residence: City	State	Country	Citizenship
Mailing Address			
City	State	ZIP	Country

☐ Additional inventors or a legal representative are being named on the ____ supplemental sheet(s) PTO/SB/02A or 02LR attached hereto.

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Application Number	
Filing Date	
First Named Inventor	MARSHALL, William E.
Group Art Unit	
Examiner Name	
Attorney Docket Number	P01936US06

I hereby appoint:

☑ Practitioners at Customer Number 22885 → *Place Customer Number Bar Code Label here*

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☐ Practitioner(s) named below:

Name	Registration Number

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I am the:

☑ Applicant/Inventor.

☐ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

SIGNATURE of Applicant or Assignee of Record

Name	William E. Marshall
Signature	William E. Marshall
Date	3-12-04

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☑ *Total of 1 forms are submitted.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	**MARSHALL, William E.**
SERIAL NO:	continuation-in-part of 09/883,550
FILED:	March 15, 2004
TITLE:	OLIGORIBONUCLEOTIDES ALERT THE IMMUNE SYSTEM OF ANIMALS TO THE IMMINENCE OF MICROBIAL INFECTION
GRP./A.U.:	1645
EXAMINER:	
CONF. NO.:	
DOCKET NO:	P01936US06

132 DECLARATION OF WILLIAM E. MARSHALL

Mail Stop Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, William E. Marshall hereby declare the following.

1. I am the inventor on the above-identified case and am familiar with the prosecution including the office action dated January 20, 2004.

2. My background includes a Ph.D. in biochemistry from the University of Illinois, post-doctoral training at Uppsala University and Cambridge University, assistant professor of biochemistry at the University of Minnesota, director of technology development at General Foods Corp., president of the Microbial Genetics Division of Pioneer Hi-Bred International, member of the Iowa Academy of Sciences, chairman of the National Agricultural Research and Extension Users Advisory Board of the U.S. Congress, member of the advisory panel on biotechnology to the Office of Technology Assessment of the U.S. Congress, member of the advisory panel on intellectual property to the GATT, and associate professor of microbiology and immunology at the New York Medical College.

3. In 1989, as president of the Microbial Genetics Division of Pioneer Hi-Bred, Int'l., Inc. I submitted a New Animal Drug Application to the Center for Veterinary Medicine of the Food and Drug Administration. The results of the Phase III trial with a probiotic in a gel were very positive but the Agency required an explanation of the cellular and molecular modes of action before permitting claims that the drug had reduced the incidence of viral shipping fever in cattle 40%. I left industry and joined the faculty of the New York Medical College for the expressed purpose of determining the modes of action.

4. Our first discovery was learning that bacteria encountering physiologic conditions release substances that absorb ultraviolet light with a maximum at 254 nm.

5. Feeding or injecting preparations of the bacteria-free released substances <10kDa to mice protected them from the lethality of a subsequent challenge of endotoxin.

6. Third, I learned that the released substances were oligoribonucleotides (ORNs) from RNA.

7. I observed that bacteria begin to accumulate these oligoribonucleotides (ORNs) concomitantly with the destruction of their ribosomes late in their growth cycle. I reasoned that the oligoribonucleotides originated from the destruction of the ribosomes.

8. I further deduced that through co-evolution the immune system adapted a learned alert response to the sudden appearance of released oligoribonucleotides. This alert response protected the host from the lethality of endotoxemia.

9. It is well established that the immune system responds to molecules that are non-mammalian in nature and origin and, to which they have been exposed during co-evolution. These molecules represent non-self. Ribosomes are ubiquitous in biology and contain sequences of RNA that are specific to their kingdoms, genera and species. I believe that the immune systems of animals have adapted a learned response, through co-evolution, to the different oligoribonucleotides that arise from the destruction of ribosomes throughout the biological world.

I believe that the alert response, which protected mice from endotoxemic death that we described in earlier applications occurs when sentry cells of the immune network detect oligoribonucleotides found only, or at a disproportionately high level in the ribosomes of bacterial cells.

Since viruses do not contain ribosomes, the alert response to bacterial oligoribonucleotides has been evolutionarily adapted to include protection against viral infections, as seen in the clinical trial mentioned in paragraph 3, above.

10. An example of oligoribonucleotides that are unique or found in disproportionately high levels in bacterial cells are the ribosomal signature sequences which differentiate the three kingdoms of microbes and are also found uniquely in certain genera and species of bacteria. Woese, C.R., 2002, On The Evolution of Cells, Proc. Natl. Acad. Sci. 99(13):8742-7. Shaver, Y. *et al.*, 2001 Variation in 16S-23S rRNA Intergenic Spacer Regions among *B. Subtilis* 168 Isolates. Molec. Microb. 42:101-10.

11. Another example is the ribosomal sequences encoded by DNA sequences that are present at levels 13 times higher in bacterial genomes than found in mammalian cells. These contain the sequence Cytosine-phosphate-Guanosine (CpG) between at least 4 or 5 adjoining bases on either side. A number of these oligodeoxynucleotides (ODNs) have been found by Kreig to activate cells of the immune system, but since ODNs are not released when bacteria enter physiologic conditions, the immune response is not a learned adaptation and their administration therefore induces adverse responses and toxicity. Kreig, A., *et al.*, 1995 CpG Motifs in Bacterial DNA Trigger Direct B-cell Activation, Nature 374:546-9 and J Immun 1998 161:2428-34.

In my opinion, administering the oligoribonucleotides that are complementary to these oligodeoxynucleotides would result in immune stimulation without adverse side effects. Some examples are:

AGAGGGUC**GC**AC**GC**GGUA (SEQ ID NO: 1) and,
CGUACU**GC**AACUCG (SEQ ID NO: 2) and,
AGGUACA**GC**CAGGACUACGA (SEQ ID NO: 3).

12. I have found that the oligoribonucleotides that are effective immune stimulants were smaller than 10kDa, i.e., containing fewer than about 33 nucleotides. Furthermore, they could not be further reduced in size by the enzyme ribonuclease. To explain this resistance, the ORNs must be double stranded, hairpins, or have groups blocking the active site or contain unusual bases or nucleotide sequences.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that

these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Date: 3-12-04

William E. Marshall

William E. Marshall